Current Application Status and Research Progress of Patient-Reported Outcomes at Home and Abroad (Postprint)

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Abstract

Patient-reported Outcome (PRO) refers to information regarding any aspect of a patient' s self-reported health status, functional status, and treatment experience, directly obtained from the patient without interpretation by healthcare professionals or any other personnel, and PRO has become the core and key component of Clinical Outcomes Assessment (COA). With the rapid development of PRO research and application, PRO has been widely utilized in recent years in clinical effectiveness evaluation, drug review and approval, health economics assessment, and other domains. This study aims to comprehensively review the cutting-edge progress and development trends of PRO both domestically and internationally, in order to provide relevant references and insights for PRO research and application in our country.

Full Text

Application Status and Research Progress of Patient-Reported Outcomes at Home and Abroad

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Abstract

Patient-reported outcome (PRO) refers to any information directly reported by patients regarding their health condition, functional status, and treatment experience, without amendment or interpretation by clinicians or other parties. PRO has become the core and key component of clinical outcomes assessment (COA). With the rapid development of PRO research and application in recent years, PRO has been widely used in clinical effectiveness assessment, drug review and approval, health economics evaluation, and other fields. This study aims to comprehensively review the frontier progress and development trends of PRO both domestically and internationally, in order to provide references for PRO research and application in China.

Key words: Patient-reported Outcome; Health Outcomes; Effectiveness Assessment

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With the development of personalized medicine and the promotion of patient-centered healthcare, patients' status and role in health decision-making have become increasingly prominent. Clinical outcomes assessment (COA) evaluates patients' feelings and functional status, mainly comprising four types: patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), and performance outcome (PerfO) [1]. PRO refers to any information directly reported by patients regarding their own health status, functional state, and treatment experience, without interpretation by healthcare professionals or others [2]. PRO primarily covers patients' symptoms, functional status, health-related quality of life, health behaviors, health preferences, treatment satisfaction, and doctor-patient communication, which can be collected through qualitative interviews, self-assessment scales, patient daily logs, and other methods [3,4].

In recent years, PRO has been widely applied in clinical effectiveness evaluation, drug review and approval, and health economics assessment [5-7]. Although domestic literature has introduced and reviewed PRO [3,4,8,9], systematic summaries and comprehensive reviews of PRO application status and development trends remain lacking. This study aims to comprehensively review the frontier progress and development trends of PRO both domestically and internationally, providing relevant references for domestic PRO research and application.

International Development and Application of PRO

In the 1980s, PRO began to be applied as an endpoint indicator in drug clinical trials [10,11]. In 2005, the European Medicines Agency (EMA) recommended using health-related quality of life (HRQoL) indicators in drug evaluation [12]. In 2006, the U.S. Food and Drug Administration (FDA) issued the "Draft Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[13]. After three years of pub-

lic consultation, the guidance was officially released in 2009, explicitly requiring the inclusion of patient-reported health outcome indicators in clinical efficacy evaluation and drug trial reporting [2]. This milestone event incorporated PRO into drug review, approval, and regulatory policies. In 2008, EMA launched a qualification program for biomarkers to approve clinical trial endpoint testing programs, with health outcome measurement tools including existing and newly developed scales [11,14]. In 2011, ruxolitinib for myelofibrosis became the first oncology drug approved in the U.S. using PRO data as a secondary endpoint [15,16]. Currently, PRO is widely applied in global drug review and approval. Approximately 26% of FDA drug reviews from 2016-2020 included PRO measurements [17], while the proportion reached 46% in EMA drug reviews from 2008-2012 [18].

PRO has been extensively used in health decision-making for drug regulation. Since 2016, the U.S. has issued the "21st Century Cures Act" and the "Patient-Focused Drug Development (PFDD) Guidance" series [1], dedicated to collecting patient experience data for drug development and review, promoting value assessment of drugs and medical devices, and maximizing the role of patient-reported data in regulatory decisions. Meanwhile, FDA initiated the qualification of COA instruments. As of August 2022, all FDA-qualified COA measurement tools were PRO instruments, covering six diseases including chronic heart failure, major depressive disorder, irritable bowel syndrome, asthma, chronic obstructive pulmonary disease, acute bacterial chronic bronchitis in COPD patients, and non-small cell lung cancer [10,19].

Beyond drug regulation, PRO is also used to assess clinical treatment effectiveness and healthcare quality. In the UK, for example, the National Health Service (NHS) incorporated PRO into its outcomes framework as an annual quality measurement item for medical institutions, collecting PRO data from patients undergoing hip replacement, knee replacement, inguinal hernia surgery, and varicose vein surgery to evaluate healthcare quality [4,20].

Health technology assessment (HTA) has gradually become an important tool for health decision-making. The UK' s National Institute for Health and Care Excellence (NICE), the U.S. FDA, and other institutions have integrated patient preference information (PPI) into comprehensive health technology evaluation systems and drug review processes to ensure decisions align with patient preferences and needs [21,22]. Currently, patient health preference information has been applied in drug development and clinical pathways to guide selection of appropriate trial endpoints, provide benefit-risk assessment information for regulators, supply reimbursement decision information for HTA agencies, and offer additional references for comprehensive government decision-making [21,22].

Health state utility (HSU) reflects patients' preferences for specific health states and represents an important component of PRO measurement, widely applied in health technology assessment and pharmacoeconomic evaluation globally [6,23]. Multi-attribute utility instruments (MAUI) are extensively used for measuring health utility values [24], making PRO a crucial basis for health resource al-

location and decision-making. By 2020, pharmacoeconomic guidelines in 35 countries and regions had specifically recommended multi-attribute health utility scales [23,25].

International PRO Research Advances

International PRO research has made substantial progress in recent years, with PRO measurement systems gradually improving and being applied in clinical and nursing practice. New developments have also emerged in health measurement tools for children and adolescents, as well as in methodological approaches for constructing health utility scales and utility scoring systems. Quality evaluation standards for PRO measurement tools, such as the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN), have matured and gained widespread application, providing robust methodological support for improving PRO research quality.

To enhance the scientific rigor and systematic nature of PRO measurement and promote flexible and diversified application scenarios, PRO measurement systems have rapidly developed and gained extensive application. In 2004, the U.S. National Institutes of Health (NIH), in collaboration with Stanford University, Duke University, Washington University, and other research organizations, developed the Patient-Reported Outcomes Measurement Information System (PROMIS) using item response theory and computer adaptive testing (CAT) to collect patient-reported information on physical, psychological, and social aspects as outcome indicators for clinical treatment evaluation [26,27]. In 2018, Dewitt et al. constructed the PROMIS-Preference (PROPr) utility scoring system based on U.S. population preferences, providing a new option for calculating health utility values [28,29].

In the field of health utility measurement, generic health utility scales such as the EQ-5D and SF-6D have been widely applied in clinical effectiveness evaluation and health economics assessment [6,23]. In 2017, the University of Sheffield formed an international research team with Australia, China, and other countries to expand the connotation of health measurement by integrating health-related quality of life with wellbeing measurement. In 2022, they developed the EQ-HWB (EQ Health and Wellbeing) scale [30-32], providing a new tool for international and cross-cultural health measurement comparisons.

Due to the rapid growth and development of children and adolescents, health measurement in this population has remained a hotspot in PRO research. Generic health-related quality of life scales such as the Pediatric Quality of Life Inventory (PedsQL™) and generic health utility scales including the Child Health Utility 9D (CHU9D) and EQ-5D-Y (Youth version) have been widely applied in child and adolescent health measurement [33,34]. Particularly, with the gradual establishment of EQ-5D-Y value sets [35-38], more appropriate options have become available for health economics evaluation in pediatric populations.

Given the wide variety and uneven quality of PRO measurement tools, quality evaluation and selection have received increasing attention. To scientifically and standardize the development and selection of PRO measurement tools, several widely used evaluation standards have been developed since the 1990s, including the Medical Outcomes Trust Scientific Advisory Committee (MOT-SAC) criteria, the Evaluating Measures of Patient-Reported Outcomes (EMPRO), and COSMIN [39]. Among these, COSMIN has become the most widely used and recognized quality evaluation standard internationally [40-42].

Domestic PRO Policies and Practice

PRO has developed rapidly in China in recent years and has been widely applied in drug review and approval, dynamic adjustment of medical insurance drug lists, and comprehensive clinical drug evaluation. In 2020 and 2021, the National Medical Products Administration (NMPA) released the "Guiding Principles for Real-World Evidence Supporting Drug Development and Review (Trial)" and the "Guiding Principles for Real-World Data Used to Generate Real-World Evidence (Trial)," which identified PRO as one of the ten common sources of real-world data [43,44].

In 2021, the Center for Drug Evaluation (CDE) of NMPA successively issued the "Guiding Principles for Clinical Value-Oriented Development of Antineoplastic Drugs" [45] and the "Technical Guiding Principles for Clinical Development of Drugs for Rare Diseases" [46], encouraging the application of PRO in drug development for rare diseases and oncology to reflect improvements in patients' quality of life and experience and their clinical value, and recommending PRO as important supportive data for primary endpoints. In January 2022, CDE officially released the "Guiding Principles for Application of Patient-Reported Outcomes in Drug Clinical Development (Trial)," establishing PRO as an important indicator in China's drug review and approval process [47]. This represents a milestone in domestic PRO research and application.

In August 2022, CDE released three clinical trial-related guiding principles including the "Technical Guiding Principles for Patient-Centered Clinical Trial Benefit-Risk Assessment (Draft for Comment)" [48-50]. These principles advocate for patient-centered drug development from design to implementation, promoting the integration of meaningful patient experience data into clinical trials to better highlight drug clinical value. From 2010-2020, 29.7% of interventional clinical trials conducted in China used PRO as primary or secondary endpoints [51], demonstrating that PRO has become an important support for drug regulatory decision-making and value assessment in China.

Since the establishment of the National Healthcare Security Administration in 2018, pharmacoeconomic evaluation has become key evidence for national medical insurance drug list access decisions [52]. Cost-utility analysis is the main method of pharmacoeconomic evaluation, with health utility values being fundamental and critical parameters that directly impact health decisions.

The "China Guidelines for Pharmacoeconomic Evaluation (2020 Edition)" recommends prioritizing generic health utility scales such as EQ-5D-3L, EQ-5D-5L, and SF-6D [25].

In 2021, the National Health Commission officially released the "Guidelines for Comprehensive Clinical Drug Evaluation (2021 Trial Edition)," aiming to comprehensively analyze drug safety, effectiveness, economy, innovation, appropriateness, and accessibility to provide evidence for improving national drug policies and ensuring rational clinical drug use [53]. The core indicators for effectiveness evaluation mainly include survival duration and quality of life, with quality-of-life indicators encompassing health-related quality of life and health utility values. This shows that PRO has become an important indicator of health benefits in China' s comprehensive clinical drug evaluation, offering a new perspective for assessing drug clinical value.

Domestic PRO Research Advances

In recent years, China has conducted considerable PRO measurement research and practice. Internationally widely used PRO measurement tools have been introduced and culturally adapted into Chinese versions, while domestic tools have been developed and health utility scoring systems based on Chinese populations have been constructed, providing effective tool support for health outcomes measurement. Domestic academic organizations and research institutions have been established, effectively promoting academic exchange and application of PRO.

China has actively introduced and translated internationally mature PRO scales while developing localized measurement tools based on Chinese populations. Widely used international scales such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [54], Diabetes Quality of Life measure (DQOL) [55], ICECAP-A capability wellbeing measure [56,57], and SF-6Dv2 [58] have been introduced domestically. Meanwhile, domestic scholars are exploring the development of localized measurement tools, including series of quality-of-life scales for cancer patients [59,60] and chronic disease patients [61], a quality-of-life scale for hepatitis B patients [62], and multiple PRO measurement tools with traditional Chinese medicine characteristics [63]. Research teams from Shandong University and other institutions are developing a health-related quality-of-life scale for Chinese infertile patients, exploring localized health measurement tools against the backdrop of national population development strategies and differences in fertility concepts between East and West [64].

Domestic research on localized health utility measurement has been actively conducted. Since 2014, utility scoring systems based on Chinese populations have been established for generic health utility scales including EQ-5D-3L [65-67], EQ-5D-5L [68], SF-6Dv2 [69], and CHU9D [70], providing localized health utility scoring systems for pharmacoeconomic models. In 2019, the China Center

for Health Development Studies of the National Health Commission, in collaboration with McMaster University in Canada and Tianjin University, established the China Health Outcomes Measurement Alliance, which has launched research on health outcomes measurement based on Chinese populations and sociocultural contexts, developing generic health utility scales for Chinese populations and disease-specific scales for cardiovascular patients [71]. In 2022, research teams from Beijing University of Chinese Medicine developed the Chinese Medicine Quality of Life Evaluation Scale (CQ-11D) based on traditional Chinese medicine theory and health concepts, and constructed a health utility scoring system for Chinese populations using discrete choice experiments with time trade-off (DCETTO), providing a localized health outcomes measurement tool for health economics evaluation in Chinese medicine [72,73].

Domestic academic institutions and organizations related to PRO research have also been established. In 2019, the PROMIS International Center-China was established at Fudan University, conducting series studies on Chinese translation and clinical application of PROMIS [74]. In 2020, Shandong University established the Health Preference Research Center, the first university-level research platform in China dedicated to health preference research, focusing on methodological and applied research in PRO measurement and health preferences [75]. In March 2021, the Health Measurement and Evaluation Professional Committee of the Chinese Preventive Medicine Association was established, providing a robust academic platform for health outcomes measurement researchers nationwide to conduct high-level academic discussions and exchanges, and promoting the dissemination and application of new theories, technologies, and methods in health outcomes measurement [76].

Trends and Prospects for PRO Research in China

With the continuous development of patient-centered drug development and healthcare service concepts and practices, along with active advocacy from national health policies, PRO research and application in China has entered a golden stage of rapid development. However, PRO application in health regulatory decision-making and clinical practice remains in its infancy, with considerable room for improvement in future research and practical application.

3.1 Strengthening Development of Localized PRO Tools Although China has developed some PRO measurement tools, domestic scales remain relatively limited, with translation and adaptation of foreign scales being the main approach. Due to significant differences in health preferences and concepts between Chinese and Western populations [77,78], we should both actively introduce mature foreign scales and develop localized measurement tools. Attention must be paid to the quality and standardization of PRO tool development, following standardized development processes and guidelines. Additionally, high-quality localized PRO data collection should be strengthened, with research designs fully considering patient representativeness, selecting appropriate and

effective PRO measurement tools, and conducting long-term cohort follow-up studies combined with disease clinical stages whenever possible.

3.2 Emphasizing Integration of PRO with Clinical Practice Future efforts should strengthen the integration of PRO with clinical practice. China is gradually exploring relevant initiatives. In January 2022, Sichuan Cancer Hospital launched a multicenter randomized controlled trial applying PRO to postoperative symptom management in lung cancer patients [79]. The study found that PRO-based proactive symptom management could effectively reduce complications and decrease medical visits and costs. This study fills the domestic gap in PRO-based perioperative management and serves as a successful example of PRO application in clinical practice. Future exploration should identify more pathways and models, particularly for cancer, mental illness, and rare disease populations. PRO-based disease symptom assessment and chronic disease management can provide more effective information for clinical and nursing practice, compensate for limitations of objective laboratory indicators, and improve patients' quality of life.

3.3 Actively Exploring Electronic Patient-Reported Outcomes (ePRO) With the maturation of digital technology and COVID-19 prevention requirements, electronic patient-reported outcomes (ePRO) will become increasingly prevalent, offering clear advantages in data collection efficiency, real-time capability, flexibility, and patient privacy protection [80]. The "Guiding Principles for Real-World Data Used to Generate Real-World Evidence (Trial)" released by CDE in April 2021 emphasized strengthening ePRO application and integrating PRO with electronic medical record systems to form complete patient-level data flows [44]. China should gradually establish ePRO information platforms and develop data collection systems for various scenarios including smartphones, tablets, and computers. For elderly or different disease populations, integrated applications with wearable medical devices and microsensors driven by digital information can provide diversified data collection models [81]. Additionally, ePRO application requires electronic migration of paper PRO tools and equivalence testing, with attention to security issues in data collection, storage, transmission, and access permissions, as well as data quality. China should also develop relevant industry standards or guidelines for ePRO use to enhance the standardization and scientific rigor of data collection [47,81].

3.4 Promoting Interdisciplinary Collaboration and Deepening PRO Research Content In terms of disciplinary development, epidemiology and health statistics, social medicine, traditional Chinese medicine, pharmacoeconomics, clinical medicine, nursing, and other disciplines are conducting PRO research, but studies remain relatively independent with insufficient exchange and lack systematic research. Future efforts should actively promote high-level academic discussions to facilitate interdisciplinary communication and integra-

tion. Regarding research content, current domestic PRO research mainly focuses on quality of life, with insufficient attention to patient compliance, health preferences, doctor-patient communication, treatment satisfaction, and patient functional status assessment. Future research should explore multi-perspective, multi-domain PRO studies centered on patient-centered service models to better serve clinical decision-making and improve healthcare quality and patient satisfaction.

Listening to patients' voices and focusing on their experiences in health decision-making both reflects basic medical ethics principles and represents the necessary path to improving healthcare quality and patient satisfaction. In recent years, China has issued multiple PRO-related policies and conducted extensive practice and exploration, with drug regulatory authorities, medical insurance departments, and health commissions all focusing on PRO research and application from different perspectives. However, China' s PRO research and application level still needs improvement. Academia, industry, and clinical institutions should strengthen collaboration to promote the organic integration of PRO research and application to better serve health decision-making, while enhancing international exchange and cooperation to actively introduce cutting-edge concepts and advanced technologies to continuously improve China' s PRO research level.

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References

[The references section contains the same bibliographic entries as provided in the original text, preserved in their original format.]

Note: Figure translations are in progress. See original paper for figures.